

**What is claimed is:**

1. A pharmaceutical formulation for pulmonary administration, the  
5 pharmaceutical formulation comprising:  
particulates comprising an active agent particle in a lipid matrix, the active  
agent having a solubility in water of less than 1.0 mg/ml;

wherein at least 90% of the active agent particles in the pharmaceutical  
formulation have a geometric diameter less than 3  $\mu\text{m}$  and wherein the particulates have a mass  
10 median diameter less than 20  $\mu\text{m}$ .

2. A pharmaceutical formulation according to claim 1 wherein the particulates  
have a mass median diameter less than 10  $\mu\text{m}$ .

3. A pharmaceutical formulation according to claim 1 wherein the particulates  
15 have a mass median diameter less than 5  $\mu\text{m}$ .

4. A pharmaceutical formulation according to claim 1 wherein at least 95% of  
the active agent particles have a geometric diameter less than 3  $\mu\text{m}$ .  
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5. A pharmaceutical formulation according to claim 1 wherein at least 50% of  
the active agent particles have a geometric diameter between 0.5  $\mu\text{m}$  and 3  $\mu\text{m}$ .

6. A pharmaceutical formulation according to claim 1 wherein at least 50% of  
25 the active agent particles have a geometric diameter between 1  $\mu\text{m}$  and 3  $\mu\text{m}$ .

7. A pharmaceutical formulation according to claim 1 wherein the lipid matrix  
comprises one or more phospholipids.

8. A pharmaceutical formulation according to claim 1 wherein the lipid matrix  
30 comprises one or more of dipalmitoylphosphatidylcholine, distearylphosphatidylcholine,

diarachidoylphosphatidylcholine dibehenoylphosphatidylcholine, diphosphatidyl glycerol, short-chain phosphatidylcholines, long-chain saturated phosphatidylethanolamines, long-chain saturated phosphatidylserines, long-chain saturated phosphatidylglycerols, and long-chain saturated phosphatidylinositols.

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9. A pharmaceutical formulation according to claim 1 wherein the particulates are hollow.

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10. A pharmaceutical formulation according to claim 1 wherein the particulates are porous.

11. A pharmaceutical formulation according to claim 1 wherein the particulates are hollow and porous.

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12. A pharmaceutical formulation according to claim 1 wherein the pharmaceutical formulation has a bulk density of less than  $0.5 \text{ g/cm}^3$ .

13. A pharmaceutical formulation according to claim 1 wherein the pharmaceutical formulation has a bulk density of less than  $0.3 \text{ g/cm}^3$ .

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14. A pharmaceutical formulation according to claim 1 wherein the pharmaceutical formulation has a bulk density of less than  $0.2 \text{ g/cm}^3$ .

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15. A pharmaceutical formulation according to claim 1 wherein the particulates are in dry powder form for aerosolization in a dry powder inhaler.

16. A pharmaceutical formulation according to claim 1 wherein the particulates are suspended in a propellant for aerosolization in a metered dose inhaler.

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17. A pharmaceutical formulation according to claim 1 wherein the particulates are suspended within a liquid for aerosolization in a nebulizer.

18. A pharmaceutical formulation according to claim 1 wherein the active agent particle is crystalline.

5 19. A pharmaceutical formulation according to claim 1 wherein the particulate further comprises a polyvalent cation.

20. A pharmaceutical formulation according to claim 1 wherein the active agent has a solubility in water of less than 0.1 mg/ml.

10 21. A pharmaceutical formulation according to claim 1 wherein the particulates are formed by spray drying.

15 22. A pharmaceutical formulation according to claim 1 wherein the insoluble active agent comprises an antimycotic agent.

23. A method of making a pharmaceutical formulation for pulmonary administration, the method comprising:

20 suspending active agent particles and a hydrophobic material in a liquid feedstock, wherein at least 90% of the active agent particles have a geometric diameter less than 3  $\mu\text{m}$ ; and

spray drying the feedstock suspension to produce particulates comprising an active agent particle at least partially in the hydrophobic material.

25 24. A method according to claim 23 wherein the feedstock comprises water and wherein the active agent has a solubility in water of less than 1.0 mg/ml.

25. A method according to claim 23 further comprising collecting the particulates.

30 26. A method according to claim 25 wherein the collected particulates have a

mass median diameter less than 20  $\mu\text{m}$ .

27. A method according to claim 25 wherein the collected particulates have a mass median diameter less than 10  $\mu\text{m}$ .

28. A method according to claim 23 wherein 95% of the active agent particles have a geometric diameter less than 3  $\mu\text{m}$ .

29. A method according to claim 23 wherein the hydrophobic material comprises a lipid.

30. A method according to claim 23 wherein the hydrophobic material comprises a phospholipid.

31. A method according to claim 23 wherein the hydrophobic material comprises a hydrophobic amino acid.

32. A method according to claim 23 further comprising adding an emulsifying agent to the feedstock.

33. A method according to claim 23 wherein the emulsifying agent comprises distearoyl phosphatidylcholine.

34. A method according to claim 23 further comprising adding a blowing agent to the feedstock.

35. A method according to claim 23 further comprising adding a polyvalent cation to the feedstock.

36. A method according to claim 23 wherein the feedstock is spray dried in a manner to produce particulates having a bulk density of less than 0.5  $\text{g/cm}^3$ .

37. A pharmaceutical formulation prepared by a method according to claim 23.

38. A pharmaceutical formulation for pulmonary administration, the  
pharmaceutical formulation comprising:  
particulates comprising an amphotericin B particle in a lipid matrix;  
wherein at least 90% of the amphotericin B particles in the pharmaceutical  
formulation have a geometric diameter less than 3  $\mu\text{m}$  and wherein the particulates have a mass  
median diameter less than 20  $\mu\text{m}$ .

39. A pharmaceutical formulation according to claim 38 wherein the  
particulates have a mass median diameter less than 10  $\mu\text{m}$ .

40. A pharmaceutical formulation according to claim 38 wherein the particulates  
have a mass median diameter less than 5  $\mu\text{m}$ .

41. A pharmaceutical formulation according to claim 38 wherein at least some of  
the particulates comprise a plurality of amphotericin B particles in a lipid matrix.

42. A pharmaceutical formulation according to claim 38 wherein the  
amphotericin B particles are crystalline.

43. A pharmaceutical formulation according to claim 38 wherein the lipid matrix  
comprises one or more phospholipids.

44. A pharmaceutical formulation according to claim 38 wherein the lipid matrix  
comprises one or more of dipalmitoylphosphatidylcholine, distearylphosphatidylcholine,  
diarachidoylphosphatidylcholine, dibehenoylphosphatidylcholine, diphosphatidyl glycerol, short-  
chain phosphatidylcholines, long-chain saturated phosphatidylethanolamines, long-chain saturated  
phosphatidylserines, long-chain saturated phosphatidylglycerols, and long-chain saturated  
phosphatidylinositols.

45. A pharmaceutical formulation according to claim 38 wherein the particulates are hollow and/or porous.

5 46. A pharmaceutical formulation according to claim 38 wherein the particulates have a bulk density less than  $0.5 \text{ g/cm}^3$ .

47. A pharmaceutical formulation according to claim 38 wherein the particulates have a bulk density less than  $0.3 \text{ g/cm}^3$ .

10 48. A pharmaceutical formulation according to claim 38 wherein the particulates have a bulk density less than  $0.2 \text{ g/cm}^3$ .

15 49. A pharmaceutical formulation according to claim 38 wherein the particulates are in dry powder form for aerosolization in a dry powder inhaler.

50. A pharmaceutical formulation according to claim 38 wherein the particulates are suspended in a propellant for aerosolization in a metered dose inhaler.

20 51. A pharmaceutical formulation according to claim 38 wherein the particulates are suspended within a liquid for aerosolization in a nebulizer.

52. A pharmaceutical formulation according to claim 38 wherein the particulates further comprise a polyvalent cation.

25 53. A pharmaceutical formulation according to claim 38 wherein the particulates are formed by spray drying.

30 54. A pharmaceutical formulation for pulmonary administration, the pharmaceutical formulation comprising:  
particulates comprising an amphotericin B particle in a lipid matrix;

wherein the particulates are hollow and/or porous and wherein the particulates have a mass median diameter less than 20  $\mu\text{m}$ .

55. A pharmaceutical formulation according to claim 54 wherein the  
5 particulates have a mass median diameter less than 10  $\mu\text{m}$ .

56. A pharmaceutical formulation according to claim 54 wherein the particulates have a mass median diameter less than 5  $\mu\text{m}$ .

10 57. A pharmaceutical formulation according to claim 54 wherein at least some of the particulates comprise a plurality of amphotericin B particles in a lipid matrix.

58. A pharmaceutical formulation according to claim 54 wherein the amphotericin B particles are crystalline.

15 59. A pharmaceutical formulation according to claim 54 wherein the lipid matrix comprises one or more phospholipids.

20 60. A pharmaceutical formulation according to claim 54 wherein the lipid matrix comprises one or more of dipalmitoylphosphatidylcholine, distearylphosphatidylcholine, diarachidoylphosphatidylcholine, dibehenoylphosphatidylcholine, diphosphatidyl glycerol, short-chain phosphatidylcholines, long-chain saturated phosphatidylethanolamines, long-chain saturated phosphatidylserines, long-chain saturated phosphatidylglycerols, and long-chain saturated phosphatidylinositols.

25 61. A pharmaceutical formulation according to claim 54 wherein the particulates have a bulk density less than 0.5  $\text{g}/\text{cm}^3$ .

30 62. A pharmaceutical formulation according to claim 54 wherein the particulates have a bulk density less than 0.3  $\text{g}/\text{cm}^3$ .

63. A pharmaceutical formulation according to claim 54 wherein the particulates have a bulk density less than  $0.2 \text{ g/cm}^3$ .

64. A pharmaceutical formulation according to claim 54 wherein the particulates are in dry powder form for aerosolization in a dry powder inhaler.

65. A pharmaceutical formulation according to claim 54 wherein the particulates are suspended in a propellant for aerosolization in a metered dose inhaler.

66. A pharmaceutical formulation according to claim 54 wherein the particulates are suspended within a liquid for aerosolization in a nebulizer.

67. A pharmaceutical formulation according to claim 54 wherein the particulates further comprise a polyvalent cation.

68. A pharmaceutical formulation according to claim 54 wherein the particulates are formed by spray drying.

69. A pharmaceutical formulation for pulmonary administration, the pharmaceutical formulation comprising:  
particulates comprising an amphotericin B particle in a lipid matrix;  
wherein the particulates have a bulk density less than  $0.5 \text{ g/cm}^3$  and wherein the particulates have a mass median diameter less than  $20 \mu\text{m}$ .

70. A pharmaceutical formulation according to claim 69 wherein the particulates have a mass median diameter less than  $10 \mu\text{m}$ .

71. A pharmaceutical formulation according to claim 69 wherein the particulates have a mass median diameter less than  $5 \mu\text{m}$ .

72. A pharmaceutical formulation according to claim 69 wherein at least some of



the particulates comprise a plurality of amphotericin B particles in a lipid matrix.

73. A pharmaceutical formulation according to claim 69 wherein the amphotericin B particles are crystalline.

74. A pharmaceutical formulation according to claim 69 wherein the lipid matrix comprises one or more phospholipids.

75. A pharmaceutical formulation according to claim 69 wherein the lipid matrix comprises one or more of dipalmitoylphosphatidylcholine, distearylphosphatidylcholine, diarachidoylphosphatidylcholine, dibehenoylphosphatidylcholine, diphosphatidyl glycerol, short-chain phosphatidylcholines, long-chain saturated phosphatidylethanolamines, long-chain saturated phosphatidylserines, long-chain saturated phosphatidylglycerols, and long-chain saturated phosphatidylinositols.

76. A pharmaceutical formulation according to claim 69 wherein the particulates are hollow and/or porous.

77. A pharmaceutical formulation according to claim 69 wherein the particulates have a bulk density less than  $0.3 \text{ g/cm}^3$ .

78. A pharmaceutical formulation according to claim 69 wherein the particulates have a bulk density less than  $0.2 \text{ g/cm}^3$ .

79. A pharmaceutical formulation according to claim 69 wherein the particulates are in dry powder form for aerosolization in a dry powder inhaler.

80. A pharmaceutical formulation according to claim 69 wherein the particulates are suspended in a propellant for aerosolization in a metered dose inhaler.

81. A pharmaceutical formulation according to claim 69 wherein the particulates

are suspended within a liquid for aerosolization in a nebulizer.

82. A pharmaceutical formulation according to claim 69 wherein the particulates further comprise a polyvalent cation.

83. A pharmaceutical formulation according to claim 69 wherein the particulates are formed by spray drying.

84. A method of making a pharmaceutical formulation for pulmonary administration, the method comprising:

suspending amphotericin B particles and a hydrophobic material in a liquid feedstock, wherein at least 90% of the active agent particles have a geometric diameter less than 3  $\mu\text{m}$ ; and

spray drying the feedstock suspension to produce particulates comprising amphotericin B at least partially in the hydrophobic material.

85. A method according to claim 84 further comprising collecting the particulates, wherein the collected particulates have a mass median diameter less than 20  $\mu\text{m}$ .

86. A method according to claim 84 further comprising collecting the particulates, wherein the collected particulates have a mass median diameter less than 10  $\mu\text{m}$ .

87. A method according to claim 84 wherein the hydrophobic material comprises a lipid.

88. A method according to claim 84 wherein the hydrophobic material comprises a phospholipid.

89. A method according to claim 84 wherein the hydrophobic material comprises a hydrophobic amino acid.

90. A method according to claim 84 further comprising adding an emulsifying agent to the feedstock.

91. A method according to claim 84 further comprising adding a blowing agent to the feedstock.

92. A method according to claim 84 further comprising adding a polyvalent cation to the feedstock.

93. A method according to claim 84 wherein the feedstock is spray dried in a manner to produce particulates having a bulk density of less than  $0.5 \text{ g/cm}^3$ .

94. A pharmaceutical formulation prepared by a method according to claim 84.

95. A method of making a pharmaceutical formulation for pulmonary administration, the method comprising:

suspending amphotericin B particles in a liquid feedstock, the liquid feedstock having a lipid and a blowing agent dissolved or suspended therein; and

spray drying the feedstock suspension to produce hollow and/or porous particulates comprising amphotericin B and the lipid.

96. A method according to claim 95 further comprising collecting the particulates, wherein the collected particulates have a mass median diameter less than  $20 \mu\text{m}$ .

97. A method according to claim 95 further comprising collecting the particulates, wherein the collected particulates have a mass median diameter less than  $10 \mu\text{m}$ .

98. A method according to claim 95 wherein the lipid comprises a phospholipid.

99. A method according to claim 95 further comprising adding an emulsifying agent to the feedstock.

100. A method according to claim 95 further comprising adding a polyvalent cation to the feedstock.

5 101. A method according to claim 95 wherein the feedstock is spray dried in a manner to produce particulates having a bulk density of less than  $0.5 \text{ g/cm}^3$ .

102. A pharmaceutical formulation prepared by a method according to claim 95.